In utero Hepatitis B Immunization during Fetal Surgery for Spina Bifida

Moehrlen, Ueli ; Elrod, Julia ; Ochsenbein-Kölble, Nicole ; Berger, Christoph ; Speck, Roberto F ; Mazzone, Luca ; Krähenmann, Franziska ; Zimmermann, Roland ; Meuli, Martin

Abstract: BACKGROUND Fetal surgery for spina bifida aperta may lead to significantly better outcomes than postnatal repair, particularly regarding shunt-dependent hydrocephalus, independent ambulation, and voiding functions. The "Management of Myelomeningocele Study" (MOMS) represents the current benchmark, also in terms of eligibility criteria. CASE REPORT A positive maternal hepatitis B virus (HBV) status is a MOMS exclusion criterion. Here, we report on the first successful active and passive in utero HBV vaccination of a spina bifida fetus carried by a HBV-positive mother undergoing maternal-fetal surgery. The now 2-year-old infant is healthy, HBV negative, and drew maximal benefit from prenatal surgery. DISCUSSION AND CONCLUSION Taken together, this patient benefitted maximally from fetal surgery for spina bifida, despite meeting an exclusion criterion. Thus, generally speaking, eligibility criteria for fetal surgery can be challenged under certain circumstances for the benefit of the patient.

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In utero Hepatitis B Immunization during Fetal Surgery for Spina Bifida

Ueli Moehrlen[a–c] Julia Elrod[a, c] Nicole Ochsenbein-Kölble[b, e]
Christoph Berger[c, d] Roberto F. Speck[f] Luca Mazzone[a–c]
Franziska Krähenmann[b, e] Roland Zimmermann[b, e] Martin Meuli[a–c]

[a]Department of Pediatric Surgery, University Children's Hospital Zurich, Zurich, Switzerland; [b]The Zurich Center for Fetal Diagnosis and Therapy, University of Zurich, Zurich, Switzerland; [c]Children's Research Center (CRC), University Children's Hospital Zurich, Zurich, Switzerland; [d]Division of Infectious Diseases and Hospital Epidemiology, University Children's Hospital Zurich, Zurich, Switzerland; [e]Department of Obstetrics, University Hospital Zurich, Zurich, Switzerland; [f]Division of Infectious Diseases and Hospital Epidemiology, University Hospital of Zurich, University of Zurich, Zurich, Switzerland

Established Facts

- In utero surgery for myelomeningocele may lead to better outcomes than postnatal repair, particularly regarding shunt-dependent hydrocephalus, ambulation, and voiding functions.
- In utero manipulation potentially increases the risk of vertical mother-to-child transmission of infectious disease, such as hepatitis B.
- The current standard postnatal immunization for hepatitis B is also highly effective in extremely premature babies.

Novel Insights

- A maternal treatment and fetal vaccination has been devised to minimize the risk of hepatitis B virus (HBV) mother-to-child transmission and thus allowing for in utero myelomeningocele repair despite a positive maternal HBV status.
- The plan includes intramuscular active and passive fetal immunization during open maternal-fetal surgery, after opening the uterus and before beginning the fetal part of the surgery. Immunization was uneventful and was well tolerated by mother and fetus.
- Generally speaking, after the quintessence of a study is published, former study criteria may be replaced by well-argued principles of personalized medicine, as this may benefit the fetus without additional risk for the mother.

Keywords
Spina bifida · Myelomeningocele · Fetal surgery · Hepatitis B · In utero immunization

Abstract
Background: Fetal surgery for spina bifida aperta may lead to significantly better outcomes than postnatal repair, particularly regarding shunt-dependent hydrocephalus, independent ambulation, and voiding functions. The "Manage-

E-Mail karger@karger.com
www.karger.com/fdt

Prof. Martin Meuli
Department of Pediatric Surgery, University Children's Hospital Zurich
Steinwiesstrasse 76
CH–8032 Zurich (Switzerland)
E-Mail martin.meuli@kispi.uzh.ch

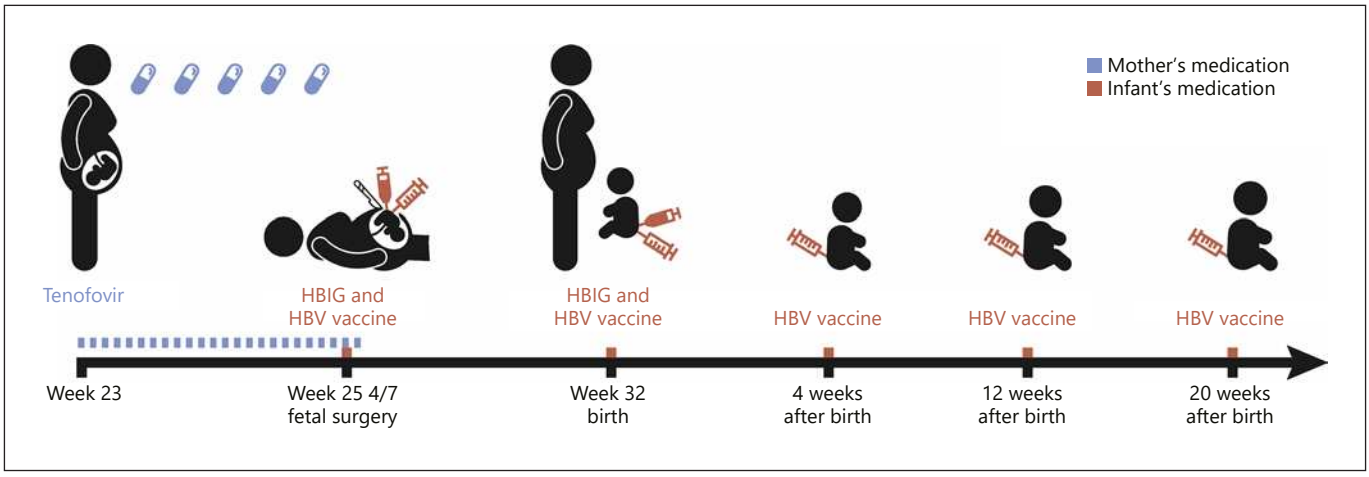

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Fig. 1. Treatment concept. Tenofovir was administered to the mother as of the 23rd week of pregnancy until after fetal myelomeningocele repair. Myelomeningocele repair was performed at 25+4 weeks of gestation, including intrauterine active and passive immunization. The newborn was actively and passively immunized within the first hour of life. Primary active immunization was completed by application of a dose at weeks 4, 12, and 20. HBIG, hepatitis B immune globulin.

ment of Myelomeningocele Study" (MOMS) represents the current benchmark, also in terms of eligibility criteria. ***Case Report:*** A positive maternal hepatitis B virus (HBV) status is a MOMS exclusion criterion. Here, we report on the first successful active and passive in utero HBV vaccination of a spina bifida fetus carried by a HBV-positive mother undergoing maternal-fetal surgery. The now 2-year-old infant is healthy, HBV negative, and drew maximal benefit from prenatal surgery. ***Discussion and Conclusion:*** Taken together, this patient benefitted maximally from fetal surgery for spina bifida, despite meeting an exclusion criterion. Thus, generally speaking, eligibility criteria for fetal surgery can be challenged under certain circumstances for the benefit of the patient.

Case Report

A clinically healthy, 29-year-old, 4th gravida, 3rd para, was referred to the Zurich Center for fetal diagnosis and therapy in July 2016 for evaluation regarding eventual fetal surgery for spina bifida. At 22+0 weeks of gestation, fetal magnetic resonance imaging and ultrasound confirmed lumbo-sacral myeloschisis (upper level lumbar 4), Chiari II malformation with cerebellar herniation (level C3), moderate bilateral ventriculomegaly (14 mm), normal fetal leg movements on both sides (including ankles), no foot deformities, and regular bladder filling. The karyotype was normal (male).

The only relevant maternal problem was chronic, most likely inactive, hepatitis B virus (HBV) infection; in fact, she was HBs antigen positive, anti-HBs negative, anti-HBc positive, BeAg negative, and anti-HBe positive, indicating chronic hepatitis B. HBV-DNA was detectable by polymerase chain reaction, but the absolute blood level was non-quantifiable (<10 U/mL), yielding a very low risk for vertical mother-to-child transmission (MTCT) [1].

Taken together, apart from maternal HBV infection, mother and fetus were good candidates for prenatal spina bifida repair.

Since the expectant parents firmly declined termination of pregnancy and definitely wanted to pursue fetal surgery, a multidisciplinary expert team, including adult and pediatric infectious disease specialists with special hepatitis expertise, devised a maternal treatment and fetal vaccination plan (Fig. 1) for minimizing the risk of HBV MTCT.

After extensive, multidisciplinary, full disclosure, non-directive prenatal counselling, informed written consent was obtained from both parents.

Prior to the operation, the mother was given a 3-week antiviral therapy with tenofovir disoproxil fumarate (TDF) 245 mg/day. Subsequently, open maternal-fetal surgery was performed at 25+4 weeks of gestation, including intramuscular active and passive fetal immunization with HBsAg (Engerix®-B 10) and HBV IgG (200 IU Hepatitis-B-Immunglobulin Behring) *after* opening the uterus and *before* beginning the fetal part of the operation (Fig. 2). Surgery and the postoperative course were uneventful until 32 weeks of gestation, when the baby was born by caesarean section due to intractable premature labor. The newborn received another dose of active and passive immunization against HBV within the first hour of life. Adaptation was normal, and the patient was discharged 9 weeks later. He demonstrated a complete regression of the formerly marked cerebellar herniation, a mild ventriculomegaly without the need for shunting, and corpus callosum dysplasia. Clinically, he showed normal voiding functions including a normal bladder manometry and normal motor function of both lower extremities.

Primary immunization was completed with additional doses of active HBV vaccine at 4, 12, and 20 weeks after birth according to the WHO recommendations [2] (Fig. 2). HBV serology at 15 months of age revealed no signs of HBV infection (HBsAg nega-

tive) and yielded an anti-HBs titer >100 IE/L (anti-HBs IgG 264 IE/L), a surrogate for full protection against hepatitis B.

At 26 months of age, the patient presented with suspected aqueductal stenosis, mild supratentorial hydrocephalus (no need for shunting), hypoplasia of the corpus callosum, and partial splenium agenesis. At the repair site, the commonly found posterior tethering and a small dermoid cyst were identified. Voiding functions and leg mobility remained normal, and independent ambulation was possible. Mental, linguistic, and fine motor development was near normal, whereas gross motor skill development was slightly delayed.

Discussion

A positive maternal HBV status is an exclusion criterion according to the current protocol (MOMS). In the present case, we decided to offer maternal-fetal surgery despite the presence of maternal HBV infection and hereby report on our approach, expose our arguments, actions, and results.

Definitely, in case of fetal rather than postnatal surgery, the risk of vertical hepatitis B transmission should not be greater than in case of postnatal care.

Normally, MTCT of HBV occurs following perinatal fetal exposure with maternal body fluids. The standard post-birth management of neonates with a HBV-positive mother would consist of active and passive immunization within the first hours of life [3, 4], which is very effective for preventing vertical HBV transmission [5–8], resulting in only 5% of all infants becoming chronic HBV carriers, equivalent to a reduction of MTCT of almost 90% [9–11].

The current standard postnatal immunization is also highly effective in premature babies: Song et al. [6] did not find any association between premature birth, low birth weight, and MTCT of HBV, and according to Omeñaca et al. [7], extremely preterm babies had a response to HBV vaccination at 2, 4, and 6 months similarly to full-term infants.

Based on the above considerations, a management plan was devised. By administering active and passive fetal immunization to the patient *after* opening the uterus and *before* beginning the fetal part of the operation, and then also immediately after birth, we aimed at providing the best possible protection from peri- and postoperative as well as from birth-related transmission. By applying this regimen, the risk of the patient to get infected with HBV appeared very low.

In addition, low maternal HBV replication as in the present case is a favorable prognostic factor [12]. Nonetheless, TDF is very effective in lowering the HBV titer [13, 14]; thus, the mother was prescribed TDF for 3 weeks.

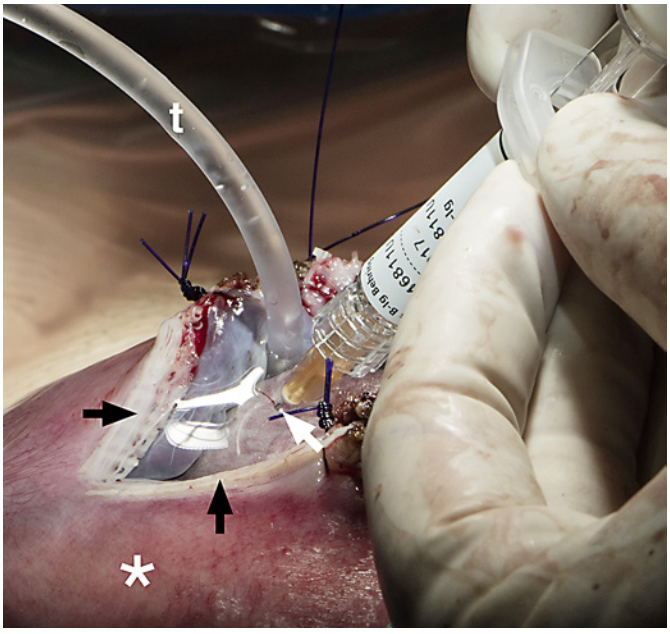

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Fig. 2. In utero immunization. Intrauterine active and passive immunization was performed via intragluteal injection (white arrow) after opening the uterus, yet before commencing any surgical procedures on the fetus so as to impede contact of the fetal circulation with the HB virus before vaccination. Black arrows are hysterotomy edges, the asterisk denotes the uterus, and t is the rubber tube to substitute amniotic fluid.

Of note, our fetal surgery scenario exactly followed the above given plan, and we did not encounter any side effects from immunization or antiviral treatment. Notably, we have a large experience using TDF in HIV-infected pregnant mothers [15], and our data support the safety of TDF-FTC backbones, initiated in pregnancy with respect to gestational length and birthweight. On the other side, TDF and the administered immunization protected the patient from potential infection with HBV, now serologically excluded at the age of 2 years.

Importantly, there is compelling experimental [16] and clinical [17, 18] evidence that fetal surgery saves neurological function. Without fetal surgery, this patient would have had an 82% probability of needing shunting for hydrocephalus [17], a high probability of having severe irreversible neuropathic bladder and rectum [19], and of being wheelchair dependent for a lifetime.

This case exemplifies that the rigorous criteria for a randomized clinical trial must not necessarily be kept in place after the quintessence of the study is published. Rather, patients may receive a more appropriate treatment and enjoy better outcomes when decision-making follows the principles of personalized medicine.

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